Remarks

Claim 1 is amended. Claims 1-14 are pending.

The 35 U.S.C. § 102(b)Rejections

The Examiner rejected claims 1-2, 4-9 and 14 under 35 U.S.C. § 102(b) for anticipation by Friede et al. U.S. Patent No. 6,558,670. This rejection is respectfully traversed.

Claim 1, as amended, recites "[a] method of enhancement of an immune response and immunomodulating activity comprising administration to a subject an effective amount of an adjuvant composition with synergistic effect comprising an iscom particle comprising fraction A of Quil A together with at least one other adjuvant, wherein the at least one other adjuvant is in free form or integrated into another separate iscom particle other than the one in which the fraction A of Quil A was integrated."

Thus, claim 1 is directed an iscom particle comprising fraction A of Quil A and a free form (i.e. not integrated into any iscom particle) of another adjuvant and to an iscom particle comprising fraction A of Quil A and an adjuvant integrated into another separate iscom particle. Therefore, the claim is not directed to an iscom particle comprising both fraction A of Quil A and at least another adjuvant. The iscom particle may be an iscom or an iscom matrix.

U.S. Pat. No. 6,558, 670 (Friede et al.) is directed to vaccines. The abstract discloses adjuvant compositions comprising a saponin and an immunostimulating ologonucleotide. The saponin may be QS 7 of Quil A (column 4 lines 13-14). It is further disclosed that the saponins may be in the form of iscoms (column 2 lines 11-18). The only example in the patent describes a mixture of Q21 of Quil A, which is close to fraction C of Quil A, and the ologinucleotide CpG. However, the Q21 fraction is not integrated into iscoms in the example.

Applicant respectfully submits that Friede et al. do not disclose that fraction A, QS 7 or Q21 must be in an iscom particle and that any other adjuvant may be in an iscom particle that must be different from the one in which fraction A is integrated.

Furthermore, U.S. Pat. No. 6,558, 670 discloses that haemolytic saponins are preferred (column 2 lines 59-62). According to the presently claimed invention, the less haemolytic saponin of Quil A is chosen, namely fraction A. This less haemolytic fraction of Quil A is furthermore always integrated into an iscom or an iscom matrix particle. In so doing, fraction A

is bound to cholesterol in the iscom or iscom matrix particle which further reduces or even eliminates the haemolytic effect. Thus, U.S. Pat. No. 6,558,670 actually teaches away from the present invention in preferring haemolytic saponins.

Hence, Applicant respectfully request withdrawal of this rejection.

The Examiner rejected claims 1, 3-4, 9-10 and 14 under 35 U.S.C. § 102(b) for anticipation by Cox et al. WO 96/11711. This rejection is respectfully traversed.

Applicant respectfully submits that WO 96/11711 cannot be cited against novelty of the instantly claimed invention. According to WO 96/11711, saponins from different Quil A fractions are integrated into the same iscom particle.

At the bottom of page 3 of the instant Office Action, the Examiner states that "[t]he method of Cox et al teaches that an iscom matrix comprising a fraction of Quil A and can have at least one immunogen (adjuvant) incorporated into or associated with the iscom matrix." However, Applicant respectfully submits that an immunogen is not an adjuvant.

Applicant respectfully submits that in immunology, an adjuvant is an agent that may stimulate the immune system and increase the response to a vaccine, without having any specific antigenic effect in itself. According to the SABIN Vaccine Institute: Antigen: Any substance, which can generate the formation of a specific antibody (a protein created by the immune system to protect the body). For vaccines, the term antigen refers to a vaccine component that induces protection for one single disease (e.g., the measles - antigen induces protection against measles). Immunogen: A substance capable of provoking an immune response; also called an antigen.

Applicant respectfully submits that WO 96/11711 does not disclose the use of adjuvants in different iscom or iscom matrix particles. Rather, WO 96/11711 relates to a saponin preparation comprising from 50%-90% by weight of Fraction A and from 50% to 10% of Fraction C of the Quil A saponins. Further, WO 96/11711 regards iscom matrix comprising the saponin preparation (claim 4) in the same iscom matrix particle.

WO 96/11711 also relates to an immunogenic iscom which comprises an iscom matrix according to any of claims 4 to 6, having at least one immunogen (i.e. not another adjuvant than fraction A and C already present) incorporated into or associated with said iscom matrix (claim 7). This is in fact an iscom complex comprising not only saponins, but also an antigen.

Applicant respectfully submits that WO 96/11711 does not disclose that the at least one immunogen(s) may be integrated into different iscom particles. Moreover, WO 96/11711 does not disclose that saponins, i.e. fraction A and C respectively of Quil A, may be integrated into different iscom matrix particles or different iscom particles.

The presently claimed invention relates to an iscom particle comprising at least one saponin chosen from fraction A of Quil A or a corresponding iscom matrix particle comprising at least one saponin chosen from fraction A of Quil A which has a general synergistic adjuvant effect when mixed with another (other) adjuvant(s). Another (other) adjuvant(s) may be in free form or integrated into another separate iscom or iscom matrix particle. The iscom and iscom matrix is defined on page 10, lines 12-23, of WO 2005/00260.

Applicant respectfully submits that WO 2005/00260 discloses the use of fraction A and fraction C of Quil A in the same iscom particle. In contrast, in the instantly claimed invention, instead of combining activities into common particles, the activities are refined by formulation into separate particles that are allowed to exert activities, target cells or organs totally independent of each other. Thus, the instant claims are novel.

Therefore, Applicant respectfully request withdrawal of this rejection.

The 35 U.S.C. § 103 Rejection

The Examiner rejected claims 1, 3 and 11-13 rejected under 35 U.S.C. § 103(a) as being unpatentable over Cox et al. (WO 96/11711). This rejection is respectfully traversed.

As discussed above, WO 96/11711 does not disclose or suggest all the elements of the instantly claimed invention.

Furthermore, Applicant respectfully submits that the synergistic effect of the presently claimed invention is, for example, depicted in Example 9 and Figure 10 of the instant specification. Figure 10-1 depicts antibody response (total IgG) to TT (Tetanus Toxoid) after immunization with 2.5 Lf of TT alone or with Monophosphoryl Lipid A (MPL) (50 or 10 μg) or a combination of QWT (fraction A of Quil A in matrix) and 10 μg MPL (A after 1st immunization and B after booster).

The adjuvant effect of Monophosphoryl Lipid A (MPL), measured as antibody response to Tetanus Toxoid (TT), is enhanced and modulated by addition of QWT- Matrix. The IgG

response after addition of QWT-Matrix to a low dose of MPL (10 μg) is higher than that of both 50 and 10 ug of MPL (Fig 10-1).

The IgG 1 response showed the same profile as the total IgG response both after the primary and second immunization.

Figure 10-2 shows antibody response (IgG2a) to TT (Tetanus Toxoid) after immunization with 2.5 Lf of TT alone or with MPL (50 or 10 μg) or a combination of QWT (fraction A of Quil A in matrix) and 10 μg MPL (A after 1st immunization and B after booster).

Mice immunized with TT adjuvanted with low dose of MPL (10 μg) supplemented with QWT-Matrix responded with 10 fold higher IgG2a titres than mice immunized with TT supplemented with low dose of MPL (10-2 A). Mice in other groups did not develop significant primary IgG2a response. Thus, the IgG2a response is strongly enhanced, indicating a synergistic, modulatory effect of QWT-Matrix and MPL.

After the booster, mice immunized with TT adjuvanted with low dose of MPL (10 μg) supplemented with QWT-Matrix responded with the highest IgG2a titres being more than 100-fold higher than mice in other groups (10-2 B).

The synergistic effects of the present invention do not only reside in the fact that numbers are increased - e.g., antibody titres are enhanced, but are also measured as a totally different type of immune modulation. Th2-biased immunomodulators, like CT, are together with Matrix-A (QWT) exerting a potent balanced Th1 **AND** Th2 response and very similar findings are made with the different types of immunomodulators demonstrated in the instant application and in present literature.

This is not self-evident to the skilled person. See, for example, Ed C. Lavelle et al. in the article "Cholera Toxin Promotes the Induction of Regulatory T Cells Specific for Bystander Antigens Modulating Dendritic Cell Activation," The Journal of Immunology 2003 (a copy of which is enclosed for the Examiner's convenience; Encl. 1). Lavelle et al. disclose that cholera toxin CT is mixed with LPS, which results in a synergetic effect for production of one cytokine i.e. IL-10 production by immature Dendritic cells (abstract, line 8), but a negative or inhibitory effect for LPS-driven production of IL-12, TNF-a, MIP1-a and MIP-1-b (abstract, lines 10-11). Results of this kind are not straight forward to anticipate for anyone working within the adjuvant field.

A better or synergistic effect residing in a stronger and more elaborate immune response of higher quality was also shown in the study of using Matrix-A and CpG according to the presently claimed invention as published in Proteomics, 7, 2007; 2172-2183 (a copy of which is enclosed for the Examiner's convenience; Encl. 2). CpG is an example of another adjuvant and is mentioned in the instant specification on page 7, line 25, and in instant claim 2. The synergistic effect of using Matrix-A and CpG was shown in a study, the results of which are published by Jim E. Eyles et al., Immunodominant Francisella tularensis antigens identified using proteome microarray" (Proteomics, 7, 2007; 2172-2183). The experiments are performed with AbISCO-100 comprising 87% of fraction -A and 17% of fraction-C in separate particles mixed with CpG.

It is evident that the tested adjuvant system Iscoms + CpG gives higher IL-2 and IFN gamma compared to iscoms and killed LVS only (Figure 4). Furthermore, it is evident that the tested adjuvant system Iscoms + CpG modulated the antibody profile markedly toward the IgG2a subclass of antibodies and that these reflect an IL-12/IFN- gamma -driven Th1 type response (page 2181 left column). A Th1-promoting adjuvant system can confer protection against highly virulent strains of F. tularensis when administrated together with a killed vaccine (page 2182 left column). Consequently, the better or synergistic effect resides in a stronger and more elaborate immune response of higher quality.

Thus, the instant claims are unobvious over the cited document. Therefore, Applicant respectfully request withdrawal of this rejection.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6905 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date: February 4, 2007
(Monday)

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 4th day of February 2008.

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